153. A host cell comprising the isolated polynucleotide of claim 149.

154. A method of producing a polypeptide comprising culturing the host cell of claim 153 under conditions such that a polypeptide is expressed, and recovering said polypeptide.

155. A composition comprising the isolated polynucleotide of claim 149 and a pharmaceutically acceptable carrier.--

Remarks

Upon entry of the foregoing amendment, claims 24-39, 43-100, 105-139 and 141-155 will be pending in the application, with claims 24, 51, 75, 84, 105, 107, 109, 111, 121, 128, 137 and 149 being the independent claims. Claims 40-42 and 140 have been canceled. Claims 24, 43, 51, 67, 75, 76, 105, 106, 107, 109, 111, 113, 121, 122, 128, 129 and 137 have been amended taking the Examiner's comments into consideration. New claims 149-155 have been added. This amendment introduces no new matter and entry thereof is respectfully requested.

Support for the amended and the new claims can be found throughout the specification. In particular, support for claims 24, 51, 105, 107, 109 and 11 can be found, *inter alia*, at pages 24-25. Support for claims 43, 67, 76, 113, 122 and 129 can be found, *inter alia*, at page 26, line 3, to page 27, line 14. Support for claim 75 can be found, *inter alia*, at page 97, line 25, to page 100, line 26. Support for claim 128 can be found, *inter alia*, at page 23, lines 9-13. Support for new claims 149-155 can be found, *inter alia*, at page 18, line 23, to page 19, line 1; and at page 27, line 27, to page 28, line 4.

These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Request for Withdrawal of Final Office Action

Applicants respectfully request reconsideration and withdrawal of the finality of the Office Action dated August 7, 2000 (Paper No. 19).[1] The circumstances under which the finality of a second or subsequent Office Action are deemed proper are set forth in M.P.E.P. § 706.07(a) at 700-39, which provides in pertinent part:

> Under present practice, second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims nor based on information submitted in an information disclosure statement filed during the period set forth in 37 C.F.R. 1.97(c) with the fee set forth in 37 C.F.R. 1.17(p).

Applicants submit that the rejection of claims 24-26, 28, 29, 31, 32, 34, 35, 37, 38, 40, 41, 43-53, 55, 56, 58, 59, 61, 62, 64, 65, 67-74, 105, 107, 109, 111 and 113-120 under 35 U.S.C. § 112, first paragraph, encompasses a new ground of rejection that was not necessitated by Applicants' amendment of the claims. In particular, the Examiner introduced a new ground of rejection at pages 7 and 8 of Paper No. 19, which could have been made previously but was not. This new ground of rejection reads:

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[1] Applicants note that the Examiner did not mark the box "This action is final" on page 2 of the Office Action summary.

> While the specification identifies useful epitopes from PDEF (SEQ ID NO:2) the claims are not limited to polynucleotides that encode polypeptides comprising or consisting of one of these epitopes. In many cases, a single amino acid substitution in one of these epitopes would be sufficient to yield an antibody (directed to the modified amino acid sequence - a new epitope) that would not bind specifically to the unmodified, original epitope. Also, even if a polypeptide comprised an unaltered epitope, extensive changes in amino acid sequence embraced by the claims would lead to other new epitopes, which in turn would yield antibodies that would not bind to the corresponding unmodified amino acid sequence. Thus, while a polyclonal antisera raised against a protein 90% identical to SEQ ID NO:2 may contain some antibodies that would bind to PDEF, it would also contain many antibodies that would not. The specification provides no utility (i.e. does not teach how to use) for such a mixed polyclonal antisera.

(Paper No. 19, at pages 7-8.)

Since the Examiner's new ground of rejection under 35 U.S.C. § 112, first paragraph, is not based on any change that resulted from the amendment of claims 24-26, 28, 29, 31, 32, 34, 35, 37, 38, 40, 41, 43-53, 55, 56, 58, 59, 61, 62, 64, 65, 67-74, 105, 107, 109, 111 and 113-120, this rejection could have been properly raised in the first Office Action (Paper No. 11). Thus, the new ground of rejection under 35 U.S.C. § 112 was not necessitated by Applicants' amendment.

In addition, the Examiner's grounds for the new rejection under 35 U.S.C. § 112 were not based on information submitted in an information disclosure statement filed during the period set forth in 37 C.F.R. § 1.97(c) with the fee set forth in 37 C.F.R. § 1.17(p).

In view of the foregoing, it is respectfully submitted that the finality of the Office Action of August 7, 2000 (Paper No. 19), is premature, and withdrawal of finality is respectfully requested.

Clarification

The Examiner indicated that the 4 sheets of Table I filed with the original application have been inserted into the specification as page numbers 103-106. However, the amendment (at page 9) indicated that there should be 5 pages to Table I to be inserted as pages 103-107. The Examiner requested clarification. (Paper No. 19, at page 2.)

Applicants made an inadvertent typographical error and meant to indicate that the 4 pages of Table I should be inserted into the specification as page numbers 103-106. Applicants regret any confusion this may have caused.

Submission of Substitute Sequence Listing

The Examiner alleged that the amendment to the paper copy of the Sequence Listing did not comply with 37 C.F.R. § 1.825(b) which requires submission of a substitute copy of the computer readable form of the Sequence Listing that incorporates the changes made to the paper copy. (Paper No. 19, at pages 2-3.)

Applicants submit that a substitute copy of the computer readable form of the Sequence Listing, which incorporated the changes made to the paper copy, was submitted on July 17, 2000. A copy of the postcard dated July 17, 2000, is submitted herewith as Exhibit A. In addition, in accordance with 37 C.F.R. § 1.825(b), Applicants state in their Amendment and Submission of Substitute Sequence Listing Under 37 C.F.R. § 1.825(a) that the copy in computer readable form is the same as the substitute paper copy of the Sequence Listing.

However, solely in an effort to advance prosecution, Applicants provide herewith a second computer readable copy of the substitute Sequence Listing filed on July 17, 2000. In accordance with 37 C.F.R. § 1.825(a), the changes that were made in the sequence listing include

no new matter, and in accordance with 37 C.F.R. § 1.825(b), the paper copy of the Sequence Listing, submitted on July 17, 2000, and the computer readable copy of the Sequence Listing, submitted herewith, are the same. Thus, this objection has been rendered moot.

Claim Objection

Claim 121 was objected to because allegedly the semicolon in line 2 is improper grammar and should be deleted. (Paper No. 19, at page 3.)

Applicants have deleted the semicolon in line 2 of claim 121. Accordingly, this objection is moot.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 137-148 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. (Paper No. 19, at page 3.) According to the Examiner, "there is no apparent support for the generic embodiment instantly claimed with respect to 'nucleotide sequence heterologous to SEQ ID NO:1' in the context of a fusion to nucleic acid encoding an epitope of PDEF." *Id.* Applicants respectfully traverse this rejection.

The Examiner is reminded that the adequate written description requirement serves to ensure that the inventor had possession, as of the filing date, of the claimed subject matter. However, "how the specification accomplishes this is not material." *In re Wertheim*, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976). Further, "[i]f a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing,

even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met." *In re Alton*, 37 U.S.P.Q. 2d 1578, 1584 (C.A.F.C. 1996).

The Federal Circuit recently reaffirmed that *ipsis verbis* description of an invention is *not* required by § 112, first paragraph. *See Union Oil Co. of California v. Atlantic Richfield Co.*, 54 U.S.P.Q.2d 1227 (Fed. Cir. 2000). ("*Unocal*"). Instead, when the skilled person could discern that the claimed invention was in applicants' possession upon reading the specification, then the written description requirement has been met. *See id.*

The specification, at page 25, lines 28-29, and at page 26, lines 3-4, teaches that any PDEF polypeptide can be used to generate fusion proteins and that examples of domains that can be fused to PDEF polypeptides include not only heterologous signal sequences, but also other heterologous functional regions. The specification further teaches, *inter alia*, at page 26, lines 14-17, that "PDEF polypeptides, including fragments and specifically epitopes, can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo." Finally, the specification teaches that "any of these above fusions can be engineered using the PDEF polynucleotides or the polypeptides." (Specification at page 27, lines 13-14.) Thus, Applicants have provided more than sufficient written description support for fusions to nucleic acids encoding epitopes of PDEF. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 75-83 remained rejected under 35 U.S.C. § 112, first paragraph, because allegedly, "the specification as originally filed provides no clear support for fragments that regulate generic 'prostate-specific epithelial gene expression'." (Paper No. 19, at page 4.) According to the Examiner, the claims should be limited to fragments that regulate expression

of the Prostate-Specific Antigen Gene. *Id.* at page 5.

Solely in an effort to advance prosecution and not in acquiescence to the Examiner, Applicants have amended claims 75-83 to recite that the fragments regulate expression of the Prostate-Specific Antigen (PSA) gene. Thus, this rejection has been rendered moot.

Claims 24-26, 28, 29, 31, 32, 34, 35, 37, 38, 40, 41, 43-53, 55, 56, 58, 59, 61, 62, 64, 65, 67-74, 105, 107, 109, 111 and 113-120 remained rejected under 35 U.S.C. § 112, first paragraph, because allegedly "the specification, while being enabling for a 'nucleic acid' that encodes SEQ ID NO:2 or a fragment of SEQ ID NO:2 (as recited in the claims), does not reasonably provide enablement for polynucleotides that do not encode SEQ ID NO:2 or a recited fragment of SEQ ID NO:2." (Paper No. 19, at page 6.)

In order to facilitate prosecution, Applicants have amended claims 24, 51, 105, 107, 109 and 111 to recite that the polypeptides encoded by the claimed polynucleotides have a specific activity of the PDEF protein recited in the specification (*i.e.*, encode polypeptides which generate antibodies that bind the full length PDEF protein). Applicants reserve the right to pursue the subject matter of the original claims in continuing applications.

Applicants note that, even in an unpredictable art, applicants are not required to disclose every species encompassed by a claim. *In re Angstadt*, 190 U.S.P.Q. 214, 218 (CCPA 1976). Further, while the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of an experiment is not a relevant consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in *In re Angstadt*, 190 U.S.P.Q. 214 (C.C.P.A. 1976):

> [If to fulfill the requirements of 112, first paragraph, an

> applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, *with reasonable certainty before performing the reaction* whether the claimed product will be obtained, . . . then *all* "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is *uncertain*. Such a proposition is contrary to the basic policy of the Patent Act.

Angstadt, 190 U.S.P.Q. at 219 (emphases in the original).

As Judge Rich explained in *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991), the statutory enablement requirement is satisfied if the specification "adequately guides the worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility." The specification of the captioned application provides such a disclosure; thus, Applicants respectfully point out that the Examiner's statements regarding "undue experimentation" are incorrect. (*See* Paper No. 19, at page 8.)

The Examiner also alleged that,

> [w]hile the specification identifies useful epitopes from PDEF (SEQ ID NO:2) the claims are not limited to polynucleotides that encode polypeptides comprising or consisting of one of these epitopes. In many cases, a single amino acid substitution in one of these epitopes would be sufficient to yield an antibody (directed to the modified amino acid sequence - a new epitope) that would not bind specifically to the unmodified, original epitope. Also, even if a polypeptide comprised an unaltered epitope, extensive changes in amino acid sequence embraced by the claims would lead to other new epitopes, which in turn would yield antibodies that would not bind to the corresponding unmodified amino acid sequence. Thus, while a polyclonal antisera raised against a protein 90% identical to SEQ ID NO:2 may contain some antibodies that would bind to PDEF, it would also contain many antibodies that would not. The specification provides no utility (i.e. does not teach how to use) for such a mixed polyclonal antisera.

(Paper No. 19, at pages 7-8.)

Applicants submit that the claims, as amended, require that the claimed polynucleotides encode a polypeptide, which generates an antibody that binds a polypeptide consisting of amino

acids 1 to 335 of SEQ ID NO:2. Thus, in order for the claimed polynucleotides to be capable of generating an antibody that binds a polypeptide consisting of amino acids 1 to 335 of SEQ ID NO:2, they should contain at least one, original, unmodified epitope. Contrary to the Examiner's assertions, it is irrelevant if changes in amino acid sequence would lead to other new epitopes, which yield antibodies that do not bind to PDEF. Even though a polyclonal antiserum raised against a protein 90% identical to SEQ ID NO:2 may contain some antibodies that do not bind to PDEF, it will also contain many antibodies that would. The amended claims do not require that *all* antibodies which are generated bind to PDEF, they only require that *an* antibody is generated that binds a polypeptide consisting of amino acids 1 to 335 of SEQ ID NO:2 (PDEF).

As Applicants discussed *supra*, although a polyclonal antiserum raised against a protein 90% identical to SEQ ID NO:2 may contain some antibodies that do not bind to PDEF, it will contain antibodies that do bind PDEF. Contrary to the Examiner's assertion that the specification does not teach how to use a mixed polyclonal antiserum, Applicants point out that the specification teaches, *inter alia*, the preparation of polyclonal antibodies at pages 64-65 (Example 11). The specification, at pages 87-88 (Example 23), also teaches, *inter alia*, that polyclonal antibodies are useful for detecting PDEF gene expression in biological samples using antibody-sandwich ELISAs. Clearly, regardless of whether a polyclonal antiserum is mixed or not, it will still be useful for detecting PDEF gene expression. Thus, one of ordinary skill in the art would clearly know how to make and use polyclonal antibodies raised against a protein 90% identical to SEQ ID NO:2.

In addition, the specification provides more than sufficient guidance regarding generating polynucleotides that encode polypeptides that are 90% identical to SEQ ID NO:2, which generate an antibody that binds to a polypeptide consisting of amino acids 1 to 335 of SEQ ID NO:2. For

example, the specification teaches that polynucleotide variants can be made, which contain alterations that produce silent substitutions, additions or deletions but do not alter the properties or activities of PDEF. (*See* specification at pages 15-16 and 18-23.) The specification further teaches the location of various antigenic epitopes within PDEF. (*See* specification at page 25, lines 10-16.) Thus, one of ordinary skill in the art would know how to routinely make polynucleotide variants, which contain alterations outside of at least one epitope, that encode polypeptides that generate an antibody that binds a polypeptide consisting of amino acids 1 to 335 of SEQ ID NO:2.

In regard to the screening of polynucleotides to identify those which fall within the scope of amended claims 24, 51, 105, 107, 109 and 111, Applicants note that a considerable amount of experimentation is permissible if it is merely routine. *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (1988). Applicants respectfully assert that the specification provides a disclosure that enables one skilled in the art to practice the claimed invention without undue experimentation. This is evidenced by the fact that, as discussed above, the specification provides guidance directed to polynucleotide variants that can be made, which retain the activity recited in amended claims 24, 51, 105, 107, 109 and 111. The captioned application thus teaches one skilled in the art to arrive at polynucleotides which fall within the full scope of amended claims 24, 51, 105, 107, 109 and 111, as well as the associated dependent claims, without undue experimentation.

In view of the above comments and claim amendments presented herein, the captioned application enables one skilled in the art to practice the full scope of the claims. Applicants thus respectfully request that the Examiner reconsider and withdraw the outstanding rejection of the claims.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 43, 67, 76, 113, 122 and 129 remained rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention, specifically for recitation of "heterologous polynucleotide." (Paper No. 19, at page 8.)

According to the Examiner, "[c]laims 46, 48, 49, 70, 72, 73, 81, 82, 116, 118, 119, 125, 127, 132, 134 and 135 as amended are definite because the claim now provides a context, i.e. relative to 'the first nucleic acid', for determining the meaning of 'heterologous regulatory sequence', i.e. it is not a regulatory sequence of the PDEF gene." *Id.*

In response, Applicants have amended claims 43 and 122 to recite "a nucleotide sequence heterologous to said first nucleic acid," and amended claims 67, 76, 113 and 129 to recite "a nucleotide sequence heterologous to said nucleic acid." Thus, withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. § 102

Claims 105-106, 113-118 and 120-148 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by GenBank Accession No. AA662204. (Paper No. 19, at page 10.) According to the Examiner, "this nucleic acid [nucleotides 3-181] is 99.4% identical to nucleotides 276-335 [sic, 1239-1420] of SEQ ID NO:1, which encodes 60 amino acids of SEQ ID NO:2." *Id.*

Applicants have amended claims 105-106 to recite a nucleic acid encoding at least 70 contiguous amino acids of SEQ ID NO:2. Support for this amendment can be found at page 18 of the specification. Nucleotides 3-181 of GenBank Accession No. AA662204 are less than 85%

identical to a polynucleotide encoding 70 contiguous amino acids of SEQ ID NO:2 (for example, a polynucleotide from nucleotides 1209-1420 of SEQ ID NO:1). Thus, this rejection has been rendered moot.

With respect to claims 121-127, the Examiner indicated that the rejection "could be overcome by inserting --over the entire length of the first nucleic acid-- before 'to a second nucleic acid'." (Paper No. 19, at page 10.)

Applicants have amended claims 121-127 accordingly. Thus, this rejection has been rendered moot.

The Examiner further noted that "[w]ith respect to claims 128-136, the prior art polynucleotide includes codons for the PA and KL dipeptides corresponding to SEQ ID NO:2 positions 298-299 and 304-304 [sic], respectively, mentioned above, which anticipates the claims when m and n are either 48 and 49, respectively, or 139 and 140, respectively." (Paper No. 19, at page 10.)

Applicants have amended claim 128 to recite that n is an integer from 141 to 335. Thus, the cited dipeptides are not encompassed by the claim. Support for this amendment can be found at pages 19-23 of the specification. Accordingly, this rejection has been rendered moot.

The Examiner further rejected claims 128-137, 140, 142-146 and 148 under 35 U.S.C. § 102(b) as allegedly being anticipated by Chen *et al.*, *Dev. Biol. 151*:176-191 (1992). (Paper No. 19, at page 11.)

With respect to claims 128-136, the Examiner noted that "the prior art polynucleotide includes the codons for the PA and KL dipeptides corresponding to SEQ ID NO:2 positions 298-299 and 304-304 [sic], respectively, mentioned above, which anticipates the claims when m and n are either 48 and 49, respectively, or 139 and 140, respectively." (Paper No. 19, at

page 11.)

As indicated *supra*, Applicants have amended claim 128 to recite that n is an integer from 141 to 335. Thus, the cited dipeptides are not encompassed by the claim. Accordingly, this rejection has been rendered moot. Applicants emphasize that the value "n is an integer from 141 to 335" is not critical to the invention. Thus, this amendment should not be construed as a surrender of equivalent embodiments wherein n is less than 141 that do not read on the cited references.

Regarding claims 137, 140, 142-146 and 148, the Examiner stated that "Chen et al. discloses [sic] vectors comprising the polynucleotide, where a heterologous promoter is operably linked to the insert, and cells comprising the vectors (page 178 through page 179, col. 1)." *Id.*

As the Examiner indicated, amino acids 71-94 of Chen's ets-4 are identical to amino acids 294-317 of SEQ ID NO:2. Applicants have amended claim 137 to exclude (c) a nucleic acid encoding amino acids 301 to 309 of SEQ ID NO:2, and have canceled claim 140. Applicants reserve the right to pursue the subject matter of original claim 140 in continuing applications. Thus, this rejection has been rendered moot.

Double patenting

The Examiner again stated that should claims 27, 30, 33, 36 and 39 be found allowable, claims 54, 57, 60, 63 and 66 would be objected to under 37 C.F.R. § 1.75 as being a substantial duplicate thereof. (Paper No. 19, at page 11.)

Upon an indication from the Examiner that claims 27, 30, 33, 36 and 39 are allowed, Applicants will consider canceling claims 54, 57, 60, 63 and 66 in an effort to advance prosecution.

Allowable Subject Matter

The indication that claims 84-100 are allowed and that claims 27, 30, 33, 36, 39, 54, 57, 60, 63, 66, 108, 110 and 112 are allowable if rewritten in independent form is noted and appreciated by Applicants.

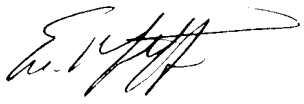
Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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Exhbit A

Due Date: July 16, 2000 (Sunday)
Today's Date: July 17, 2000 (Monday)

Applicant: LIBERMANN *et al.*

Art Unit: 1632
Examiner: Priebe, S.
Docket: 1488.1090000/EKS/GLL
Atty: EKS

Application No.: 09/126,945
Filed: July 31, 1998
For: **Prostate Derived Ets Factor**

When receipt stamp is placed hereon, the USPTO acknowledges receipt of the following documents:

1. PTO Transmittal Letter (*in duplicate*);
2. Fee Transmittal Form (PTO/SB/17) (*in duplicate*);
3. Petition For Extension of Time Under 37 C.F.R. § 1.136(a)(1) (*in duplicate*);
4. Third Supplemental Information Disclosure Statement and Fee Under 37 C.F.R. § 1.97(c) (*in duplicate*);
5. Amendment and Submission of Substitute Sequence Listing Under 37 C.F.R. § 1.825(a);
6. Paper and computer readable copy of Sequence Listing;
7. Amendment and Reply Under 37 C.F.R. § 1.111;
8. Executed Declaration for Deposited Biological Materials;
9. One return postcard; and
10. Our check no. 28117 for $368.00 to cover:
    $110.00 for one month Extension of Time fee;
    $240.00 for Submission of an Information Disclosure Statement; and
    $18.00 for excess claim fee.

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